

REMARKS

I. Status Summary

Claims 1-3, 5-10, and 12-19 are pending in the present application and have been examined by the U.S. Patent and Trademark Office (hereinafter "the Patent Office").

Claims 1-3, 5-10, and 12-17 have been rejected under 35 USC § 103(a) upon the contention that the claims are unpatentable over U.S. Patent No. 5,252,466 to Cronan (hereinafter "Cronan") in view of Rigaut *et al.* (1999) 17 *Nature Biotech* 1030-1032 (hereinafter "Rigaut").

Claims 1 and 9 have been amended. Support for the amendment can be found throughout the specification as filed, including particularly in original claims 4 and 11 (the methods of claims 1 and 9, respectively, further comprising identifying any binding partners of said protein of interest in said complexes). Additional support can be found at page 4, lines 9-10, 17-22, and 28-30; and at page 9, lines 18-21. Thus, no new matter has been added by the amendments to the claims

Reconsideration of the application as amended and in view of the remarks presented hereinbelow is respectfully requested.

II. Response to the Rejection under 35 U.S.C. § 103

Claims 1-3, 5-10, and 12-17 have been rejected under 35 USC § 103(a) upon the contention that the claims are unpatentable over Cronan in view of Rigaut. The Patent Office's assertions with respect to Cronan are presented on pages 6-7 of the Non-Final Official Action. The Patent Office concedes that Cronan does not teach identifying any binding partners that bind to a protein of interest in a complex, or cleaving the protein of interest from the post-translational modification sequence prior to identifying binding partners of the protein of interest.

The Patent Office asserts that these deficiencies are cured by Rigaut as set forth on page 7 of the Non-Final Official Action. From this, the Patent Office contends that one of ordinary skill in the art would have been motivated to combine the teachings of Cronan with the teachings of Rigaut because affinity tagging allows for rapid purification of proteins, especially heteromeric complexes, including proteins interacting with other

proteins. The Patent Office further contends that it would have been obvious to one of ordinary skill in the art to use affinity tagging for purification because these affinity tags do not impair function and allow for efficient recovery. The Patent Office thus asserts that given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention that the skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that when considering the patentability of claimed subject matter, the Patent Office is required to view both the cited art and the claimed subject matter as a whole. As set forth in M.P.E.P. § 2141.02, "[i]n determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious". Additionally, M.P.E.P. § 2141.02 also specifies that "[d]istilling an invention down to the 'gist' or 'thrust' of an invention disregards the requirement of analyzing the subject matter 'as a whole'."

Applicants respectfully submit that the Patent Office appears to be viewing the presently disclosed subject matter and the cited references improperly in that the differences between the claimed subject matter and the cited art are not being given appropriate consideration. Particularly, applicants respectfully submit that the Patent Office has not appropriately considered the nature of the binding partners, the functions that the various components of the claimed methods have, or the purposes of the claimed methods.

To elaborate, the Patent Office asserts that the antibodies disclosed in Cronan qualify as "binding partners" because the instant specification defines "binding partners" to include, in some embodiments, antibodies. Applicants respectfully submit that this assertion fails to take into account that instant independent claims 1 and 9 recite methods for obtaining *in vivo* binding partners of a protein of interest. Given that the antibodies employed in the method of Cronan are supplied by and known to the person practicing the method, applicants respectfully submit that one of ordinary skill in the art would clearly understand that purifying the fusion protein of Cronan with an antibody or

other affinity reagent that has already been isolated and characterized would not be viewed as obtaining any binding partners through the claimed method. Thus, applicants respectfully submit that Cronan does not support a rejection of claims 1 and 9 under 35 U.S.C. § 103(a).

Turning now to independent claim 16, applicants respectfully submit that this claim recites screening a plurality of potential binding partners for binding to a protein of interest. Since the Patent Office asserts that the binding partner disclosed in Cronan is the antibody that is employed for affinity purifying the fusion protein disclosed therein, applicants respectfully submit that Cronan does not disclose a screening method because the binding partner is already known. For this additional reason, applicants respectfully submit that Cronan does not support the instant rejection.

Stated another way, applicants respectfully submit that the Patent Office is apparently not appreciating that the instantly claimed methods are directed to obtaining in vivo binding partners and/or screening for in vivo binding partners. Applicants respectfully submit that one of ordinary skill in the art upon consideration of the instant specification as a whole would understand that the antibodies employed in Cronan are not binding partners that are obtained or screened for, and thus the use of such antibodies merely to purify the fusion proteins does not support a rejection of the instant claims.

Continuing with the instant rejection, applicants respectfully traverse the Patent Office's assertion on page 4 of the Non-Final Official Action that the claims are not directed to binding partners that bind to the protein of interest at areas other than the post-translational modification. Initially, applicants respectfully submit that the language of the claims makes clear that the protein of interest *per se* does not include the post-translational modification. Rather, the post-translational modification and the protein of interest make up the fusion protein. This can be seen in the language of claims 1, 9, and 16, which recite *inter alia* obtaining a cell transformed to express a fusion protein, said fusion protein comprising (i) a protein of interest; and (ii) a single post-translational modification sequence.

Applicants further respectfully submit that upon review of the instant specification, one of ordinary skill in the art would also understand that the "binding

partners” are molecules that bind to the protein of interest and not to the affinity tag. This can be determined by consideration of the express language of the claims. To reiterate, applicants respectfully submit that claims 1, 9, and 16 recite *inter alia* that the fusion protein comprise (i) a protein of interest; and (ii) a single post-translational modification sequence. Thus, the fusion protein includes at least two components: a protein of interest and a post-translational modification sequence.

In Cronan, the alleged binding partner is disclosed to be an antibody that binds to the fusion protein via the post-translational modification sequence. This is in contrast to the subject matter of the instant claims. As set forth in step (e) of claims 1 and 9 and step (f) of claim 16, the present claims recite identifying any binding partners that bind said protein of interest in said complex.

As a result, applicants respectfully traverse the Patent Office’s assertion that Cronan discloses a method for obtaining *in vivo* binding partners of a protein, since the claims clearly recite that the binding partners must bind to the “protein of interest” component of the fusion protein. There is no disclosure of any such binding partners in Cronan, and thus the Patent Office appears to be misinterpreting this reference and/or not considering each and every element of the claims as is required by M.P.E.P. § 2143.03 (“All words in a claim must be considered in judging the patentability of that claim against the prior art.” *quoting In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)).

Furthermore, applicants respectfully submit that Cronan discloses that the purpose of the post-translational modification sequence/affinity tag is to permit the fusion protein to be “identified or isolated by means of the post-translational modification” (see Cronan at col. 9, lines 7-10; emphasis added). Applicants respectfully submit that if the post-translational modification allows the fusion protein to be identified or isolated, this would require that a reagent that binds to the post-translational modification (*i.e.*, a “binding partner” according to the Patent Office) would already be known. This is precisely what is disclosed in Cronan in that the molecules asserted to be “binding partners” in Cronan (*i.e.*, the anti-tag antibodies, avidin, streptavidin, etc.) are known, and the post-translational modifications are chosen beforehand to coincide with such known reagents.

This also is in contrast to the subject matter of claim 1, 9, and 16. In each case, a reagent is used in the separating step that is different from a “binding partner” since the reagent binds to the post-translational modification sequence and the claims state that the binding partners bind to the protein of interest. Therefore, applicants respectfully traverse the Patent Office’s contention that Cronan discloses a “binding partner” as that phrase is employed in the instant claims.

Applicants further respectfully traverse the Patent Office’s assertions with respect to combining Cronan with Rigaut. The Patent Office asserts that one of ordinary skill in the art would have been motivated to combine Rigaut to the teachings of Cronan because “affinity tagging allows for rapid purification of proteins”. Applicants respectfully submit, however, that the fusion proteins of Cronan already include an affinity tag (e.g., the biotin), and thus one of ordinary skill in the art would not have been motivated to look to Rigaut to provide an affinity tag.

Furthermore, assuming *arguendo* that one of ordinary skill in the art were to look to employ an affinity tag as disclosed in Rigaut in the fusion protein of Cronan, applicants respectfully submit that the skilled artisan would have replaced the biotination sequence in the construct of Cronan with such an affinity tag. Applicants respectfully submit, however, that if one of ordinary skill in the art were to do so, then the resulting construct would no longer include encode a post-translational modification sequence, which is an element of each of independent claims 1, 9, and 16. Therefore, applicants respectfully submit that if Cronan and Rigaut were combined as suggested by the Patent Office, the resulting construct would not be useful in the methods of claims 1, 9, and 16.

And finally, applicants respectfully traverse the Patent Office’s apparent assertion that one of ordinary skill in the art would have been motivated to:

perform a method for obtaining *in vivo* binding partners of a protein comprising obtaining a cell and expressing a fusion protein comprising a protein of interest and a post-translational modification sequence; growing the cell under conditions to permit expression and modification; contacting the cell extract with an affinity purification reagent; separating the complex from the extract; and identifying any binding partners, with the fusion protein being a heterologous protein, and a cleavage site between the protein of interest and the post-translational sequence, and to use a fusion

protein comprising an affinity purification sequence, wherein the purification sequence is an *S. aureus* protein A IgG binding domain or a calmodulin binding peptide.

See Non-Final Official Action at pages 7-8 (emphasis added). Applicants respectfully submit that the Patent Office has identified no basis for concluding that one of ordinary skill in the art would have been motivated to employ an *S. aureus* protein A IgG binding domain or a calmodulin binding peptide in the fusion protein of Cronan. Even assuming *arguendo* that the use of affinity tagging allows for rapid purification of proteins, the Patent Office has not articulated any basis for concluding that one of ordinary skill in the art would have been motivated to employ both a post-translational sequence and a further affinity purification sequence since the post-translational modification sequence of Cronan already is specifically designed to act as an affinity purification sequence.

Accordingly, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of claims 1, 9, and 16 over the combination of Cronan and Rigaut. Claims 2, 3, 5-8, 10, 12-15, and 17 all depend directly or indirectly from one of claims 1, 9, and 16, and thus are also believed to be distinguished over the cited combination. As a result, applicants respectfully submit that claims 1-3, 5-10, and 12-17 are now in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

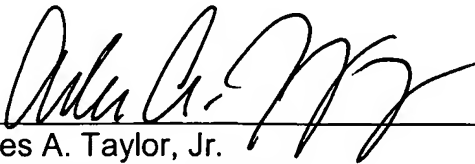
The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

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